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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,336	01/10/2006	Cornelis Marius Timmers	2002.750US	8846

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
07/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,336	TIMMERS ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4-7, 9-13, 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7, 9-13, 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4-7, 9-13, 16 are pending in the current application.

2. This application is a national stage of PCT/EP03/51025 filed November 16, 2003 which claims priority to U. S. Provisional Application 60/435,040 filed December 20, 2002 and European Union Application (EPO) 2102866.7, filed December 20, 2002.

Claim Rejections/Objections Withdrawn

3. The rejections of claims 1, 4-7, 9-13, 16 under 112 1st paragraph for scope of enablement is withdrawn based upon the submission of data and arguments of counsel. R6 is only ever exemplified as phenyl, furan and thiophene. R7 "heteroaryl" has been exemplified as phenyl, pyridine, furan, and isoxazole and the R8 and R9 "heterocycloalkyl", as piperazine, pieridine, morpholine and pyrrolidine. It should be possible to make some other compounds and based on the data submitted activity as FSH ligands would likely be maintained.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

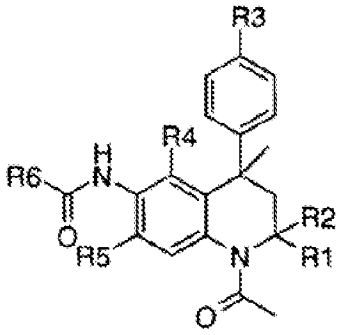
4. The rejection of method claim 16 for lack of enablement with respect to the "methods of fertility regulation" has been amended to recite "contraception in a female", and this new more narrow limitation will be addressed again below. The declaration by Cornelius Marius Timmers (the "Timmers declaration") submitted previously has admitted that the examples described in the application have a wide variety of pharmacological activity as agonist, antagonist or both for the FSH receptor. The claimed method would seem to require in the very least that such compounds be antagonists at the receptor. This declaration is an admission on the record that compounds under the scope of the instant method claims fail to have the property of FSH

antagonism. Regardless, the correlation between antagonism of the FSH receptor and "contraception in a female" has not been shown as demonstrated by the cited references.

With respect to the double patenting rejections of claims 1, 4-7, 9-13, 16, applicant's representative has argued that the 10/482,707 application claims do not overlap. This appears to be the case, since the '707 application has had numerous amendments, however anticipation type double patenting is not the only type of obviousness type double patenting. There need not be literal overlap in the claims. The examiner followed the course set forth in MPEP 804 Definition of Double Patenting:

"A double patenting rejection of the obviousness-type>, if not based on an anticipation rationale,< is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. In re Braithwaite, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, *>the< analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis."

It may be that a further explanation is needed. The instant claim 1 is shown below:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^3 are H or Me

R^3 is H, hydroxy, (1-4C)alkoxy,

R^4 is H, OH, or (1-4C)alkoxy,

R^5 is OH, (1-4C)alkoxy or R^7,

with the proviso that if R^4 is H, R^5 is not OH or (1-4C)alkoxy

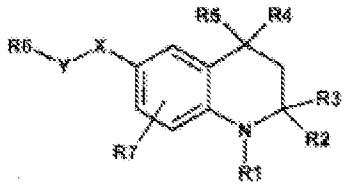
R^6 is (2-5C)heteroaryl, (6C)aryl, (3-8C)cycloalkyl, or (1-6C)alkyl, wherein the (2-5C)heteroaryl and the (6C)aryl are optionally substituted with one or more substituents selected from hydroxyl, amino, halogen, phenyl, (1-4C)alkyl, (1-4C)alkoxy, or (1-4C)(di)alkylamino,

R^7 is amino, (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, R^8-(2-4C)alkoxy, R^9-methylamino or R^9-methoxy

R^8 is amino, (di)(1-4C)alkylamino, (2-6C)heterocycloalkyl, (2-6C)heterocycloalkylcarbonylamino, or (1-4C)alkoxycarbonylamino and

The copending genus of current claim 4 (as of April 13, 2009),

) A tetrahydroquinoline compound of Formula I,



Formula I

R^1 is (1-6C)alkylcarbonyl;

R^2 and R^3 are (1-4C)alkyl;

R^4 is phenyl, optionally substituted with one or more substituents selected from the group hydroxy, f (1-4C)alkoxy;

R^5 is (1-4C)alkyl;

Y-X is C(O)-NH,

R^6 is (1-6C)alkyl, (3-9C)heteroaryl

or phenyl, wherein phenyl is optionally substituted with

R^7 is H, (1-4C)alkyl, or (1-4C)alkoxy;

Since instant claim 1 has an apparent proviso there is not literal overlap, however the instant claims are drawn to compounds that have a very strong structural similarity the 10/482,707 application compounds, including the exemplified species claimed.

No argument for patentability of claims 1, 4-7, 9-13, 16 with respect to the double patenting rejection over the 10/540,335 application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper

timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1, 4-7, 9-13, 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4, 7, 10-21, 23 of copending Application No. 10/482,707. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope substantially and cover the same compounds. The wording is only slightly different and the '707 application is broader but where X is NH and Y is CO the compounds of the instant case are produced. It is noted that some of the same species are present in both applications.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Van Straten et. al. teaches numerous compounds of the instant case that amount to change of the position of substituents, or other minor variations available within the general teaching.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Van Straten et. al. evidently do not expressly teach the compounds of the instant case, based on a proviso, but the general teaching provides the compounds of the instant case that are only minor variations.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare the compounds of the instant case. The compounds of the claims at hand are analogs of old compounds. One of ordinary skill would be motivated to make the compounds of the invention because he would expect the compounds to have similar properties, indeed we see that these compounds have the same properties. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more

a *prima facie* case may be made", *In re Deuel* 34 USPQ2d 1210, "a known compound may suggest its **analogs** or isomers, either geometric isomers (*cis* v. *trans*) or position isomers (emphasis added) (*e.g. ortho v. para*)".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. The applications appear to have a common assignee.

5. Claims 1, 4-7, 9-13, 16 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 11 of copending Application No. 10/540,335. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims overlap in scope substantially and cover the same compounds. The wording is only slightly different and the '335 application is narrower but the genus produced is nearly identical. It is noted that some of the same species are present in both applications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention. The claims are drawn to "methods of …….contraception in a female", however no clear nexus exists between the compounds described here and "contraception in a female". In the words of van Straten et. al. (pg. 1700 conclusion) these compounds "may serve as starting points for further optimization to evaluate the feasibility of FSH receptor antagonists as a novel method for contraception."

The effect physiologically of a compound that binds and perturbs the FSH-R (a GPCR) is unclear. While knockout mice are clearly sterile ("Genetic elimination of the alpha subunit in mice by homologous recombination (7) causes complete deficiency of all three glycoprotein hormones, and animals of both sexes are not only sterile but also hypothyroid." M. Ram Sairam and Hanumanthappa Krishnamurthy "The Role of Follicle-Stimulating Hormone in Spermatogenesis: Lessons from Knockout Animal Models" Archives of Medical Research 32 (2001) 601–608.) Mutants which presumably have some receptor function (as in the instant case) "exhibit delayed sexual maturity and reduced fertility".

FSH receptor signaling is very complex as evidenced by Alfredo Ulloa-Aguirre et. al. "Role of the intracellular domains of the human FSH receptor in GαS protein coupling and receptor expression." *Molecular and Cellular Endocrinology* **2007**, 260–262, 153–162.

"The human FSHR consists of 695 amino acids (the first 17 amino acids encoding the signal sequence) (Simoni et al., 1997; Ulloa-Aguirre and Timossi, 1998; Dias et al., 2002); upon activation by agonist, the activated receptor may trigger activation of a number of intracellular signaling pathways. In the classical, linear signaling cascade, occupancy of the FSHR causes activation of the heterotrimeric Gs protein, which in turn stimulates the effector adenylyl cyclase with the consequent increase in the synthesis of the second messenger cAMP, activation of PKA, phosphorylation of cAMP response element-binding protein, and activation of transcription (Reichert and Dattatreyamurty, 1989). Nevertheless, **increasing evidence indicates that in addition to the adenylyl cyclase/cAMP/PKA signaling pathway, activation of the FSH receptor by its cognate ligand also triggers activation of other intracellular signaling cascades, including the MAPK and PI3-K/Akt pathways** (Cameron et al., 1996; Maizels et

al., 1998; Gonzalez-Robayna et al., 2000; Richards et al., 2002; Seger et al., 2001)..... **In contrast to the related TSHR and LHR, there is a paucity of structure-function data on the role of the intracellular domains in FSHR-mediated signal transduction** and receptor expression."

"Although the hFSHR preferentially couples to the Gsα-subunit, there is some experimental evidence suggesting that the FSHR may additionally signal through the pertusis toxin-sensitive Gi/o-mediated pathways (Eskola et al., 1994; Arey et al., 1997; Timossi et al., 1998). In this regard, alternative spliced variants of the receptor may be one of the mechanisms by which particular intracytoplasmic domains of the FSHR may signal through these G proteins (Sairam et al., 1997). As mentioned above, the FSHR also signals through cAMP- dependent, but PKA-independent alternate signaling cascades (Richards et al., 2002); in addition, it has been shown that the adapter protein 14-3-3τ, a member of the 14-3-3 protein family which play a key role in signal transduction pathways, cell division and apoptosis (Tzivion and Avruch, 2002), interacts with the iL2 of the hFSHR, suggesting a role for this cytoplasmic protein in FSHmediated cAMP independent signaling (Cohen et al., 2004). APPL1, another adapter protein that interacts with the p110α catalytic subunit of PI3K and with inactive Akt (Mitsuuchi et al., 1999), has been more recently identified as an hFSHR iL1-interacting partner, providing a potential link between the FSHR and the PI3K/Akt signaling pathway (Nechamen et al., 2004). One thus may envision a complex system of multiple, pleiotropic signals triggered by the activated FSHR, in which compartmentalization and oligomerization of particular receptor populations may potentially play fundamental roles." Pg. 159

One reviewer summarized the state of the art this way: "Only in the clinic will the question of whether small molecule LHR and FSHR modulators will be successful as fertility-regulating agents be answered." (Guo, Tao "Small molecule agonists and antagonists for the LH and FSH receptors." Expert Opinion on Therapeutic Patents 2005 15(11) 1555-1564, conclusions.) See the MPEP 2164.02 for the correlation of in-vitro to in-vivo testing. There is no successful use of these compounds in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome, thus undue experimentation would be required. The real problem here is that this receptor is a GPCR with a vast number of binding sites and conformations each of which may be associated with a distinct physiological outcome. One reviewer has summarized the situation this way (Terry Kenakin and Ongun Onaran "The

ligand paradox between affinity and efficacy: can you be there and not make a difference?" *TRENDS in Pharmacological Sciences* **2002**, *23*, 275-280):

"A probabilistic model of protein conformation can be used to quantify the probability of various receptor conformations and the effect of ligand binding on those conformations. The basic idea behind the probabilistic model is that the function of a receptor protein is not assigned to particular conformations of the receptor. Instead, the function arises as a result of ligand-induced perturbation of the distribution of conformational states over the conformational space of the receptor……..**The foregoing discussion leads to the general conclusion that if a ligand binds to the receptor, it most probably will produce a bias in the conformations of the receptor ensemble** [i.e. it will change the receptor by its presence (Fig. 3)]. Therefore, this suggests that all ligands with macro-affinity should be extensively studied for pharmacological activities other than simple G-protein activation because various physiological activities have been defined that are mediated by conformations not necessarily related only to G-protein activation…… Ligand activities that are not related to a standard G-protein-mediated physiological response **might have therapeutic utility**.

Here we have exactly this situation, namely a ligand with affinity, and very limited information about the function, which as Kenakin et. al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility."

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone

number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625